Respiratory Medicine (2011) 105, 1946–1953

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Adaptive servo-ventilation improves renal function in patients with heart failure

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Received 12 April 2011; accepted 4 September 2011
Available online 28 September 2011

KEYWORDS
Adaptive servo-ventilation;
Chronic kidney disease;
Heart failure;
Sleep-disordered breathing

Summary
Background: Impaired cardiac function and sleep-disordered breathing (SDB) are associated with progression of chronic kidney disease (CKD) in heart failure (HF) patients. Adaptive servo-ventilation (ASV) therapy improves cardiac function in HF patients regardless of the SDB severity through hemodynamic support and prevention of repetitive hypoxic stress. This study was designed to test the hypothesis that ASV therapy improves renal function in HF patients with SDB.
Methods and results: Of 59 consecutively enrolled HF patients, 43 with moderate-to-severe SDB underwent ASV therapy. HF patients were divided into the ASV-treated group ($n = 27$) and the non-ASV-treated group ($n = 16$). Estimated glomerular filtration rate (eGFR), echocardiographic parameters, and inflammatory biomarkers were measured before and 12 months after ASV initiation. Improvement in the eGFR was found in the ASV-treated group, but not in the non-ASV-treated group. There was a positive correlation between the increases in eGFR and left ventricular ejection fraction ($r = 0.488$, $p = 0.001$). The changes in high-sensitivity C-reactive protein were negatively correlated with change in the eGFR ($r = -0.416$, $p = 0.006$).
Conclusions: ASV therapy could improve renal dysfunction in HF patients through hemodynamic support. Additionally, prevention of SDB with the use of ASV therapy could exert anti-inflammatory effects, which could contribute to the improvement of renal function in HF patients.

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doi:10.1016/j.rmed.2011.09.001

Introduction

Chronic kidney disease (CKD) is highly prevalent and closely associated with a high mortality rate in heart failure (HF) patients.[1] Some mechanistic links between HF and CKD have been proposed; for instance, low cardiac output under HF conditions elicits prerenal insufficiency.[2] The development of novel therapeutic approaches for HF patients with CKD is desirable.

Sleep-disordered breathing (SDB) is highly prevalent and also contributes to poor prognosis in HF patients.[3] The presence of SDB enhances inflammatory responses due to repetitive hypoxic responses, leading to impairment of renal functions and progression of CKD. Impaired kidney function enhances the activity of the sympathetic nervous system and the renin-angiotensin-aldosterone system.[2,4] Therefore, the cessation of this vicious cycle could be an important therapeutic target in HF patients with CKD.

Adaptive servo-ventilation (ASV) (Autoset CS®, ResMed, Sydney, Australia) automatically adjusts its settings based on an analysis of the patient's breathing effort and maintains steady minute ventilation without hemodynamic disadvantages in HF patients. The ASV device prevents unstable breathing and increases in preload while HF patients are in the supine position. Our previous studies have shown the beneficial effects of ASV in patients with HF. First, ASV treatment increased cardiac function in HF patients with SDB by preventing the inflammatory response caused by repetitive cessation of breath.[5] Second, ASV therapy improves the short-term prognosis of HF patients and cardiac pump function regardless of the severity of SDB.[6] Therefore, improvement of cardiac function and prevention of hypoxic responses by ASV therapy could increase renal functions in HF patients. This study was designed to test the hypothesis that ASV therapy could improve renal function in patients with HF by increasing the cardiac pump function and inhibiting repetitive cessation of breathing.

Methods

Study population

This study enrolled 59 consecutive HF patients (New York Heart Association [NYHA] functional class II or III). Renal function was measured based on the estimated glomerular filtration rate (eGFR). The eGFR value was calculated using the equation of the modification of the diet in renal disease study, which was arranged for Japanese individuals and recommended by the Japanese Society of Nephrology.[7] The eGFR (ml/min/1.73 m^2) $= 194 \times$ [serum creatine]$^{-1.094} \times$ [age]$^{-0.287} \times$ [0.739 if patient is female]. CKD was defined as an eGFR of $<$60 ml/min/1.73 m^2. These patients were referred for overnight polysomnography (PSG) to screen for SDB at our sleep center of Akita University Hospital. All patients provided written informed consent regarding the PSG analysis and the ASV therapy. A previous study showed that 43% of HF patients undergoing continuous positive airway pressure (CPAP) therapy did not experience reduced AHI score.[8] The ASV therapy could eliminate SDB events effectively when compared to CPAP therapy.[9] Based on these reports, an ASV device was used to treat of HF with SDB and CKD in this study. This study was approved by the clinical research and ethics committee of the University of Akita. Patients were included in this study for the following reasons: (1) a hospital admission history due to worsening HF in the 6 months prior to therapy initiation, and (2) CHF with an ejection fraction below 55% as measured by ultrasonic echocardiography. Patients with infectious disease, pharyngeal disease, or decompensated HF, and those who had recovered from acute HF were excluded from this study.

Study design

The 59 enrolled HF patients were divided into two groups according to the severity of their SDB. The first group consisted of HF patients whose apnea hypopnea index (AHI) score was $\geq$15/h (patients with moderate-to-severe SDB, $n = 43$); the second group consisted of HF patients whose AHI score was $<$15/h (patients with non-to-mild SDB, $n = 16$). ASV therapy was initiated for the patients with moderate-to-severe SDB after admission. The patients were fitted with an ASV device, and the determination was made as to whether they would receive ASV treatment during the initial 3 days of their admission. Some patients refused ASV treatment because of the discomfort of wearing a mask or because of the positive airway pressure. Consequently, the patients with moderate-to-severe SDB were divided into 2 groups: (1) those receiving ASV treatment (ASV-treated patients; $n = 27$) and (2) those not receiving ASV treatment (non-ASV-treated patients; $n = 16$). ASV therapy was initiated the day after conventional PSG by experienced physicians. Biophysical markers (high-sensitivity C-reactive protein [hs-CRP] and plasma brain natriuretic peptide [BNP]) were evaluated, and echocardiographic parameters and eGFR were measured before and after the 12-month ASV treatment in both groups. Prescriptions for the enrolled patients were unchanged during the follow-up period. If enrolled patients experienced a decrease in blood pressure (systolic blood pressure $<$ 100 mmHg) or increased blood pressure (systolic blood pressure $>$ 140 mmHg), calcium antagonists or diuretics were decreased or added by half-increments. Additionally, if HF patients experienced a minimum of 3 kg body weight decrease or a minimum of 3 kg body weight increase, diuretics were decreased or added, respectively by half-increments. The angiotensin-converting enzyme inhibitor or angiotensin receptor blocker doses were not changed during the follow-up period due to their strong effect on renal function.

Sleep study

Enrolled patients underwent overnight PSG monitoring using the ProFusion PSG® Sleep Diagnostic System (Compumedics, Victoria, Australia), which continuously acquires the data of an electroencephalogram, electrooculogram, oxygen saturation (SaO_2), airflow, snoring, and thoracoabdominal motion. Apnea was defined as an absence of inspiration for $\geq$10 s, and obstructive apnea was distinguished from the central type by analyzing chest and abdominal motions. Hypopnea was defined as a $\geq$30% reduction in monitored airflow accompanied by a decrease

in SaO_2 of $\geq$4%. Arousal responses were defined according to the recommendations of the American Sleep Disorders Association. The AHI was defined as the number of apnea and hypopnea episodes per hour during sleep. An AHI score of $\geq$5/h was defined as SDB. A diagnosis of moderate-to-severe SDB was assigned an AHI of $\geq$15/h, and non-to-mild SDB was assigned an AHI of $<$15/h. A diagnosis of central sleep apnea was assigned to an AHI $>$15/h, with $>$50% of the events labeled as the central type rather than the obstructive type of apnea.

ASV treatment

After the PSG analysis, each patient selected a mask and was trained by an experienced sleep technician on the principles and use of the ASV system (Autoset CS®; ResMed). Adjustments were made by physicians who were familiar with ASV treatment. An expiratory positive airway pressure of approximately 5 cm H_2O and an inspiratory pressure support between 3 and 10 cm H_2O were used. Over the first 20 min of treatment, the patient's heart rate, SaO_2, and blood pressure were monitored and observed every 5 min. The ASV-treated patients were defined as those whose device usage was $>$4 h per night during the follow-up period. Compliance data were downloaded from the ASV device and checked monthly in the outpatient clinic. Patients with insufficient ASV use during sleep were entered into the non-ASV group. These patients were observed without ASV treatment during the follow-up period.

Echocardiography

Two-dimensional, M-mode, and Doppler echocardiography (iE33; Philips Medical Systems, Andover, MA, USA) were performed to evaluate various parameters of heart function in the patients. The left ventricular ejection fraction (LVEF) was determined from an apical 4-chamber view using Simpson's method. The sonographers were blinded to the PSG results and were not involved in the treatment of these patients.

Statistical analysis

Continuous variables are expressed as the mean $\pm$ standard deviation. For continuous and normally distributed data, Student's *t*-test was used for comparisons between groups; for non-normally distributed data, the Mann–Whitney *U*-test was used. Correlations were analyzed using Pearson's correlation coefficient. Stepwise multiple linear regression analyses were used to identify the influential parameters for the eGFR changes. All parameters with $p < 0.10$ in the univariate analyses were entered into the multivariate analysis. A p value of $<$0.05 was considered statistically significant. All statistical analyses were performed with SPSS for Windows ver. 16.0 (SPSS, Chicago, IL, USA).

Results

Baseline characteristics of the enrolled 59 HF patients are summarized in Table 1. AHI score ([patients with moderate-to-severe SDB] 32.3 $\pm$ 17.2 *vs.* [those with non-to-mild SDB] 10.2 $\pm$ 3.6, $p < 0.001$), hypopnea events ([patients with moderate-to-severe SDB] 18.5 $\pm$ 10.0 *vs.* [those with non-to-mild SDB] 5.1 $\pm$ 2.7, $p < 0.001$), arousal index ([patients with moderate-to-severe SDB] 30.5 $\pm$ 15.9 *vs.* [those with non-to-mild SDB] 19.3 $\pm$ 6.4, $p < 0.001$), and hs-CRP levels ([patients with moderate-to-severe SDB] 0.24 $\pm$ 0.17 mg/dl *vs.* [those with non-to-mild SDB] 0.16 $\pm$ 0.14 mg/dl, $p = 0.036$) were higher, whereas eGFR ([patients with moderate-to-severe SDB] 44.3 $\pm$ 12.7 ml/min/1.73 m^2 *vs.* [those with non-to-mild SDB] 52.8 $\pm$ 11.9 ml/min/1.73 m^2, $p = 0.033$) was lower in HF patients experiencing moderate-to-severe SDB. The eGFR in each HF patient with moderate-to-severe SDB was less than 60 ml/min/1.73 m^2.

ASV therapy was initiated in patients with moderate-to-severe SDB. Consequently, 27 patients agreed to continue ASV treatment (ASV-treated patients) and successfully underwent ASV during the 12-month follow-up period, whereas 16 patients declined the therapy (non-ASV-treated patients) or had insufficient ASV use because of mask intolerance ($n = 9$) or subjective intolerance to positive airway pressure ($n = 7$). The baseline characteristics in HF patients with or without ASV therapy are demonstrated in Table 2. No significant differences were found in either group. In the moderate-to-severe SDB group, 67% undergoing the ASV therapy were diagnosed with predominant central sleep apnea. Various parameters, including laboratory data, echocardiographic findings, and eGFR were recorded before and 12 months after ASV treatment. The non-ASV-treated patients were also observed, and the same parameters were measured.

No patient experienced potential complications or changed the study protocol during the follow-up period. Before ASV treatment, no significant differences were observed in mean age, gender ratio, the prevalence of structural heart disease, pharmacological treatment (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, diuretics, aldosterone antagonists, or statins), echocardiographic parameters, PSG data, or laboratory data between the two groups. The ASV-treated patients continued ASV treatment during the follow-up period after their hospital stay. The mean ASV device use time was 5.8 $\pm$ 0.8 h in patients undergoing ASV therapy. The non-ASV-treated patients were also observed during the follow-up period. Two patients (7.2%) in the ASV-treated patients, and one patient (6.2%) in the non-ASV-treated patients experienced increased doses of calcium antagonists, whereas one patient (3.7%) had a case of a discontinued calcium antagonist in the ASV-treated patients and one patient (6.2%) had a case of discontinued use of a calcium antagonist in the non-ASV-treated patients. Each patient (ASV-treated patients; 3.7%, non-ASV-treated patients; 6.2%) experienced increased doses of diuretics, whereas two patients (7.2%) experienced a decreased dose of diuretics in the ASV-treated patients and one patient (6.2%) was given a decreased dose of diuretics in the non-ASV-treated patients.

Table 1 Baseline characteristics of the enrolled HF patients.

	All patients ($N = 59$)	moderate-to-severe SDB-patients ($N = 43$)	non-to-mild SDB-patients ($N = 16$)	*P* Value
Age, years	74.1 ± 8.3	75.0 ± 7.1	71.5 ± 10.5	0.257
Male sex, *n* (%)	49 (83.1)	36 (83.7)	13 (81.3)	0.823
BMI, kg/m^2	23.8 ± 3.7	23.4 ± 3.1	24.9 ± 4.9	0.145
NYHA class II, *n* (%)	34 (57.6)	24 (55.8)	10 (62.5)	0.770
Hypertension, *n* (%)	50 (84.7)	38 (88.4)	12 (75.0)	0.236
Diabetes mellitus, *n* (%)	16 (27.1)	10 (23.3)	6 (37.5)	0.329
Hyperlipidemia, *n* (%)	19 (32.2)	12 (27.9)	7 (43.7)	0.348
Underlying heart disease, *n* (%)				
Ischemic heart disease	17 (28.8)	11 (25.6)	6 (37.5)	0.519
Valvular heart disease	13 (22.0)	10 (23.3)	3 (18.8)	0.707
Cardiomyopathy	18 (30.5)	11 (25.6)	7 (43.8)	0.212
Heart rhythm disorder, *n* (%)				
Atrial fibrillation	24 (40.7)	19 (41.2)	5 (31.3)	0.552
Pacemaker	17 (28.8)	11 (25.6)	6 (37.5)	0.519
Blood pressure				
Systolic, mmHg	115.8 ± 16.7	116.1 ± 16.4	115.1 ± 18.0	0.785
Diastolic, mmHg	63.5 ± 10.6	63.1 ± 9.8	64.6 ± 12.9	0.864
Heart rate,/min	66.4 ± 8.4	65.9 ± 8.4	67.6 ± 8.5	0.599
Medication, *n* (%)				
ACEIs/ARBs	57 (96.6)	42 (97.7)	15 (93.8)	0.472
β-blockers	46 (78.0)	32 (74.4)	14 (87.5)	0.481
Aldosterone antagonists	37 (62.7)	28 (65.1)	9 (56.3)	0.558
Diuretics	37 (62.7)	28 (65.1)	9 (56.3)	0.558
Ca antagonists	30 (50.8)	21 (48.8)	9 (56.3)	0.771
Statins	27 (45.8)	18 (41.9)	9 (56.2)	0.386
Polysomnography data				
AHI, *n*/*h*	26.4 ± 17.7	32.3 ± 17.2	10.2 ± 3.6	<0.001
Central, *n*/*h*	5.6 ± 10.1	6.9 ± 10.5	2.3 ± 2.6	0.066
Obstructive, *n*/*h*	4.5 ± 10.7	5.2 ± 12.3	2.4 ± 3.3	0.411
Hypopnea, *n*/*h*	14.9 ± 10.5	18.5 ± 10.0	5.1 ± 2.7	<0.001
Mean SaO_2, %	94.0 ± 2.2	94.1 ± 2.4	93.8 ± 1.6	0.683
Arousal index, *n*/*h*	27.4 ± 14.8	30.5 ± 15.9	19.3 ± 6.4	<0.001
Total Sleep Time, *h*	5.1 ± 1.0	5.1 ± 1.0	5.2 ± 1.0	0.585
Echocardiography data				
LVEF (%)	43.9 ± 9.1	44.4 ± 7.8	42.5 ± 11.9	0.979
Laboratory data				
eGFR (ml min^{-1} 1.73 m^{-2})	46.6 ± 12.5	44.3 ± 12.7	52.8 ± 9.97	0.032
hs-CRP levels (mg/dl)	0.22 ± 0.16	0.24 ± 0.17	0.16 ± 0.14	0.036
Plasma BNP levels (pg/ml)	269.1 ± 301.4	292.8 ± 328.3	205.3 ± 208.4	0.261

Values are reported as mean ± standard deviation.
HF = heart failure; SDB = sleep-disordered breathing; BMI = body mass index; ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; AHI = apnea hypopnea index; SaO_2 = oxygen satuation; LVEF = left ventricular ejection fraction; eGFR = estimated glomerular filtration rate; hs-CRP = high-sensitivity C-reactive protein, BNP = brain natriuretic peptide.

The eGFR changes of the two groups before and 12 months after ASV treatment are compared in Fig. 1 (Fig. 1, left; ASV-treated patients; Fig. 1, right; non-ASV-treated patients). The eGFR increased significantly in the ASV-treated group (44.2 ± 12.3 ml/min/1.73 m^2 to 48.2 ± 12.9 ml/min/1.73 m^2, $p = 0.0095$), but significantly decreased in the non-ASV-treated patients (44.7 ± 13.7 ml/min/1.73 m^2 to 38.3 ± 14.4 ml/min/1.73 m^2, $p = 0.0052$). The levels of eGFR at 12 months after ASV therapy were significantly elevated in the ASV-treated patients when compared to the non-ASV-treated patients (48.2 ± 12.9 *vs.* 38.3 ± 14.4 ml/min/1.73 m^2, $p = 0.0253$).

The LVEF changes before and 12 months after ASV therapy are shown in Fig. 2. An increased LVEF was observed in ASV-treated patients (Fig. 2, left; 43.5 ± 6.9% to 48.0 ± 6.5%, $p < 0.0001$), whereas a significant decreased LVEF changes were shown in non-ASV-treated patients (Fig. 2, right; 46.1 ± 9.2% to 43.8 ± 9.2%, $p = 0.0037$). Additionally, the LVEF of ASV-treated patients at 12 months after the therapy was significantly higher when compared to that of non-ASV-treated patients (48.0 ± 6.5% *vs.* 43.8 ± 9.2%, $p = 0.0322$, respectively). The reduced hs-CRP levels were observed in ASV-treated patients (0.22 ± 0.13 to 0.06 ± 0.04 mg/dl, $p < 0.001$),

Table 2 Baseline characteristics of the HF patients with moderate-to-severe SDB.

	All patients ($N = 43$)	ASV-treated patients ($N = 27$)	non-ASV-treated patients ($N = 16$)	P Value
Age, years	75.0 ± 7.1	74.8 ± 7.6	75.4 ± 6.4	0.785
Male sex, *n* (%)	36 (83.7)	23 (85.2)	13 (81.3)	0.473
BMI, kg/m^2	23.4 ± 3.1	23.4 ± 3.1	23.3 ± 3.2	0.937
NYHA class II, *n* (%)	24 (55.8)	16 (59.3)	8 (50.0)	0.565
Hypertension, *n* (%)	38 (88.4)	25 (92.6)	13 (81.3)	0.326
Diabetes mellitus, *n* (%)	10 (23.3)	6 (22.2)	4 (25.0)	0.840
Hyperlipidemia, *n* (%)	12 (27.9)	7 (25.9)	5 (31.3)	0.715
Underlying heart disease, *n* (%)				
Ischemic heart disease	11 (25.6)	6 (22.2)	5 (31.3)	0.523
Valvular heart disease	10 (23.3)	7 (25.9)	3 (18.8)	0.601
Cardiomyopathy	11 (25.6)	6 (22.2)	5 (31.3)	0.523
Heart rhythm disorder, *n* (%)				
Atrial fibrillation	19 (41.2)	11 (40.7)	8 (50.0)	0.565
Pacemaker	11 (25.6)	5 (18.5)	6 (37.5)	0.206
Blood pressure				
Systolic, mmHg	116.1 ± 16.4	117.0 ± 14.2	114.6 ± 20.0	0.643
Diastolic, mmHg	63.8 ± 9.9	62.3 ± 10.8	66.3 ± 7.7	0.206
Heart rate,/min	65.9 ± 8.4	65.8 ± 8.5	66.1 ± 8.6	0.751
Medication, *n* (%)				
ACEIs/ARBs	42 (97.7)	27 (100)	15 (93.8)	0.333
β-blockers	32 (74.4)	18 (66.7)	14 (87.5)	0.106
Aldosterone antagonists	28 (65.1)	16 (59.3)	12 (75.0)	0.307
Diuretics	28 (65.1)	16 (59.3)	12 (75.0)	0.307
Ca antagonists	21 (48.8)	13 (48.1)	8 (50.0)	0.909
Statins	18 (41.9)	10 (37.0)	8 (50.0)	0.424
Polysomnography data				
AHI, *n*/*h*	32.3 ± 17.2	32.2 ± 17.1	32.4 ± 17.8	0.979
Central, *n*/*h*	6.9 ± 10.5	5.5 ± 9.3	9.3 ± 11.4	0.571
Obstructive, *n*/*h*	5.2 ± 12.3	5.7 ± 13.0	4.5 ± 11.3	0.781
Hypopnea, *n*/*h*	18.5 ± 10.0	19.3 ± 10.1	17.3 ± 10.2	0.497
Mean SaO_2, %	94.1 ± 2.4	94.0 ± 2.5	94.2 ± 2.1	0.705
Arousal index, *n*/*h*	30.5 ± 15.9	30.9 ± 15.6	29.8 ± 16.9	0.824
Total Sleep Time, *h*	5.1 ± 1.0	5.1 ± 1.2	5.0 ± 0.8	0.783
Echocardiography data				
LVEF (%)	44.4 ± 7.8	43.5 ± 6.9	46.1 ± 9.2	0.341
Laboratory data				
hs-CRP levels (mg/dl)	0.24 ± 0.17	0.22 ± 0.13	0.28 ± 0.21	0.269
Plasma BNP levels (pg/ml)	292.8 ± 328.3	334.8 ± 389.0	222.0 ± 176.3	0.547

Values are reported as mean ± standard deviation.
HF = heart failure; SDB = sleep-disordered breathing; ASV = adaptive servo-ventilation; BMI = body mass index; ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; AHI = apnea hypopnea index; SaO_2 = oxygen satuation; LVEF = left ventricular ejection fraction; hs-CRP = high-sensitivity C-reactive protein, BNP = brain natriuretic peptide.

but not in non-ASV-treated patients (0.28 ± 0.21 to 0.30 ± 0.24 mg/dl, $p = 0.117$). The hs-CRP levels of ASV-treated patients at 12 months after the therapy initiation were reduced when compared to non-ASV-treated patients (0.06 ± 0.04 *vs.* 0.30 ± 0.24 mg/dl, $p < 0.001$, respectively). No body weight (BW) or body mass index (BMI) changes were observed in either group during the follow-up period (ASV-treated patients: [BW] 62.0 ± 8.1 to 61.5 ± 7.8 kg, $p = 0.344$, [BMI] 23.4 ± 3.1 to 23.2 ± 3.0, $p = 0.369$, non-ASV-treated patients: [BW] 63.1 ± 10.1 to 62.4 ± 9.6 kg, $p = 0.195$, [BMI] 23.3 ± 3.2 to 23.1 ± 3.0, $p = 0.242$, respectively).

Fig. 3 shows the correlation between LVEF changes and eGFR changes in patients with CHF accompanied by CKD. The changes in eGFR and the changes in LVEF were positively correlated in patients with HF ($r = 0.488$, $p = 0.001$, $R^2 = 0.283$). Fig. 4 shows the relationship between the change in eGFR and hs-CRP levels in those patients with CHF accompanied by CKD; these were negatively correlated ($r = -0.416$, $p = 0.006$, $R^2 = 0.273$). In the stepwise multiple linear regression analysis including ASV therapy use, changes in LVEF, and changes in hs-CRP levels, the ASV device use was the most influential parameter on the improvement of changes in eGFR ($\beta = 0.529$, standard

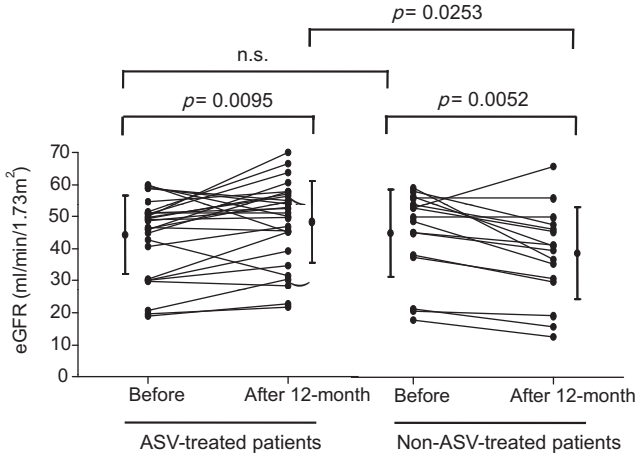

Figure 1 Comparison of the eGFR before and 12 months after ASV initiation in HF patients with or without ASV therapy. ASV-treated patients; $n = 27$, non-ASV-treated patients; $n = 16$. eGFR = estimated glomerular filtration rate, HF = heart failure, ASV = adaptive servo-ventilation.

error = 2.620, $p < 0.001$). The duration of daily ASV use did not affect the changes in eGFR ($\beta = -0.189$, $p = 0.345$) or the LVEF changes ($\beta = -0.194$, $p = 0.351$).

Discussion

This study provides several major insights into SDB as a therapeutic target in HF patients with renal dysfunction. First, the value of eGFR was significantly lower in HF patients with moderate-to-severe SDB, as compared with that in patients with non-to-mild SDB. This result suggests that the prevalence of SDB might be a contributor to renal dysfunction in HF patients (Table 1). Second, the 12-month ASV treatment improved the eGFR value in HF patients with SDB (Fig. 1). Third, the changes in the LVEF were positively

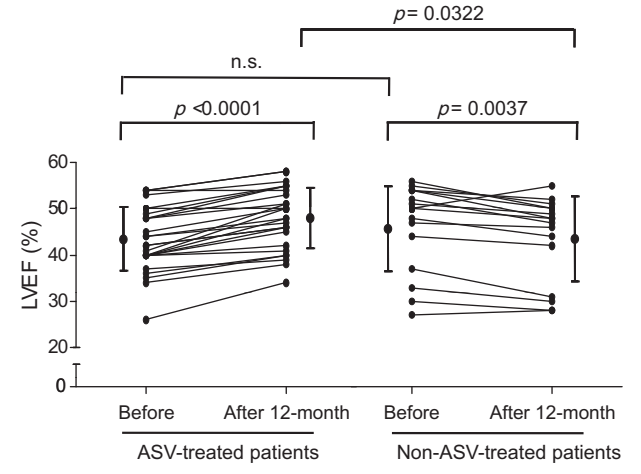

Figure 2 Comparison of the LVEF before and 12 months after ASV initiation in HF patients with or without ASV therapy. ASV-treated patients; $n = 27$, non-ASV-treated patients; $n = 16$. LVEF = left ventricular ejection fraction, HF = heart failure, ASV = adaptive servo-ventilation.

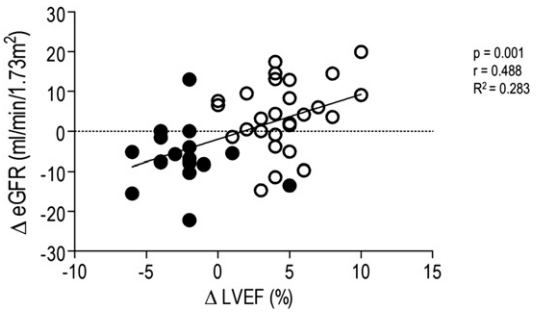

Figure 3 Correlation between the changes in eGFR and the changes in LVEF in patients with HF accompanied by CKD. Open dots; ASV-treated patients ($n = 27$), filled dots; non-ASV-treated patients ($n = 16$). eGFR = estimated glomerular filtration rate, LVEF = left ventricular ejection fraction, HF = heart failure, CKD = chronic kidney disease.

correlated with the changes in eGFR (Fig. 3), implying that the improvement in the LVEF by ASV therapy (Fig. 2) could lead to increased renal perfusion in HF patients with CKD. Finally, the changes in serum hs-CRP levels were negatively correlated with the changes in eGFR. It is likely that ASV therapy could improve renal function by preventing inflammatory responses, which might be associated with SDB (Fig. 4).

It has previously been reported that the prevalence of CKD is associated with poor prognosis in HF patients.[1] The low cardiac output due to HF leads to reduced renal perfusion,[10] endothelial dysfunction,[11] and systemic inflammation,[12] resulting in the development and progression of CKD.[2] A pharmacological approach, such as the use of diuretics, could also be a contributing factor for worsening renal dysfunction in HF patients.[10] Renal damage causes the stimulation of sympathetic nerve activity, enhancement of the renin-angiotensin-aldosterone system, and the progression of anemia, resulting in decreasing cardiac functions and worsening of the prognosis in HF patients.[2] Therefore, the prevention of this vicious cycle could be an important therapeutic approach for HF patients with CKD. Despite the fact that the development of

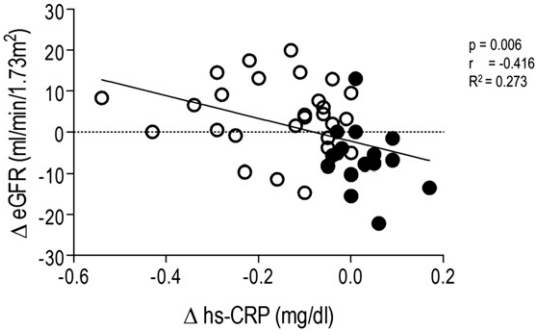

Figure 4 Correlation between the changes in LVEF and the changes in hs-CRP levels in patients with HF accompanied by SDB. Open dots; ASV-treated patients ($n = 27$), filled dots; non-ASV-treated patients ($n = 16$). LVEF = left ventricular ejection fraction, hs-CRP = high-sensitivity C-reactive protein, HF = heart failure, SDB = sleep-disordered breathing.

pharmacological and non-pharmacological therapy for CHF has improved the prognosis in HF patients, the presence of CKD still contributes to a high mortality rate, even in HF patients who have undergone these pharmacological and non-pharmacological therapies.[1,13]

It was recently reported that ASV therapy improves both the cardiac pump function without hemodynamic disadvantages and the prognosis in HF patients, regardless of the severity of SDB.[6] This result provided a novel therapeutic paradigm in that ASV therapy could be part of a hemodynamic support system in HF patients. In this study, the changes in LVEF were positively correlated with the changes in eGFR, indicating that improvements in cardiac pump function could be associated with the increase of renal function in HF patients with CKD (Fig. 3). It is likely that renal perfusion is increased by ASV therapy. Elevated sympathetic nerve activities in the failing heart could play an important role in the development and progression of CKD.[4] Another considerable reason for the improvement of renal function by ASV therapy is the prevention of sympathetic nerve activity. A recent study demonstrated that ASV therapy could immediately decrease sympathetic nerve activity in HF patients.[14] Further studies are needed to clarify the causative relationship between the reduction of sympathetic nerve activity by the ASV therapy and the improvement of renal function.

ASV therapy improves cardiac function and performance states in HF patients with SDB by preventing inflammatory responses.[5] Repetitive hypoxic stress caused by SDB could induce systemic inflammation,[5] increased sympathetic nerve activitiy[15] and endothelial dysfunction, and subsequent renal damage could develop in these patients. It is known that proinflammatory cytokines can impair renal function.[16] In the present study, changes in hs-CRP levels were negatively correlated with changes in eGFR (Fig. 4). The reduction in serum hs-CRP levels may be a surrogate marker for the improvement of inflammatory responses induced by SDB. This result implies that ASV therapy improves renal function by preventing hypoxic stress caused by SDB. Inhibition of SDB by ASV therapy could be a novel, important therapeutic option in HF patients with CKD.

Limitations of this study are as follows; first, the serum levels of cytokines such as interleukin-6 and tumor necrosis factor-α in order to assess the systemic proinflammatory responses caused by HF and repetitive hypoxia were not evaluated in this study. Second, sympathetic nerve activity was not examined in this study. Therefore, direct relationships between the improvement of renal function and the inflammatory response or sympathetic nerve activity were not clarified in this study. Third, other factors including better adherence to drug treatment may contribute to the improved renal function in ASV-treated patients. Fourth, this study could not show the prognosis of HF patients with CKD. Further randomized studies are needed to resolve these limitations.

In conclusion, ASV therapy could improve renal function by the improvement of cardiac function and prevention of SDB in patients with HF accompanied by CKD. The polymodal beneficial effects of ASV therapy constitute useful non-pharmacological therapeutic approaches to the treatment of HF patients with CKD, and could improve the prognosis of HF patients.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rmed.2011.09.001.

Conflict of interest statement

All authors declare no conflict of interest.

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